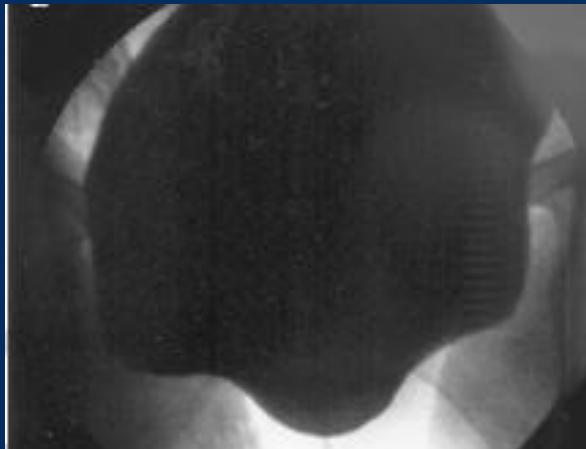


# **UAB Therapeutic Targets**

Pradeep Tyagi Ph.D.  
University of Pittsburgh

# Clinical Outcomes

UAB

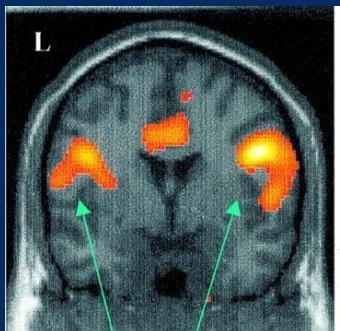
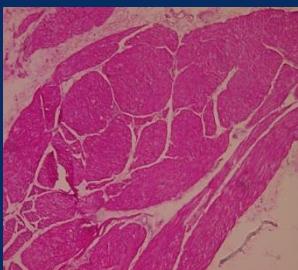
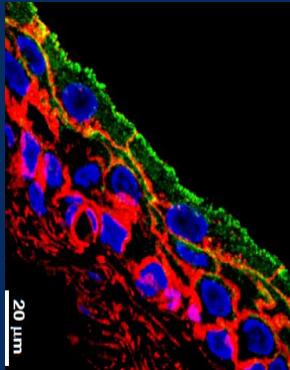


Normal



- ❖ Reduce PVR by 50%
- ❖ Reduce outlet resistance
- ❖ Increase bladder contractility
- ❖ Reduce recurrent UTI

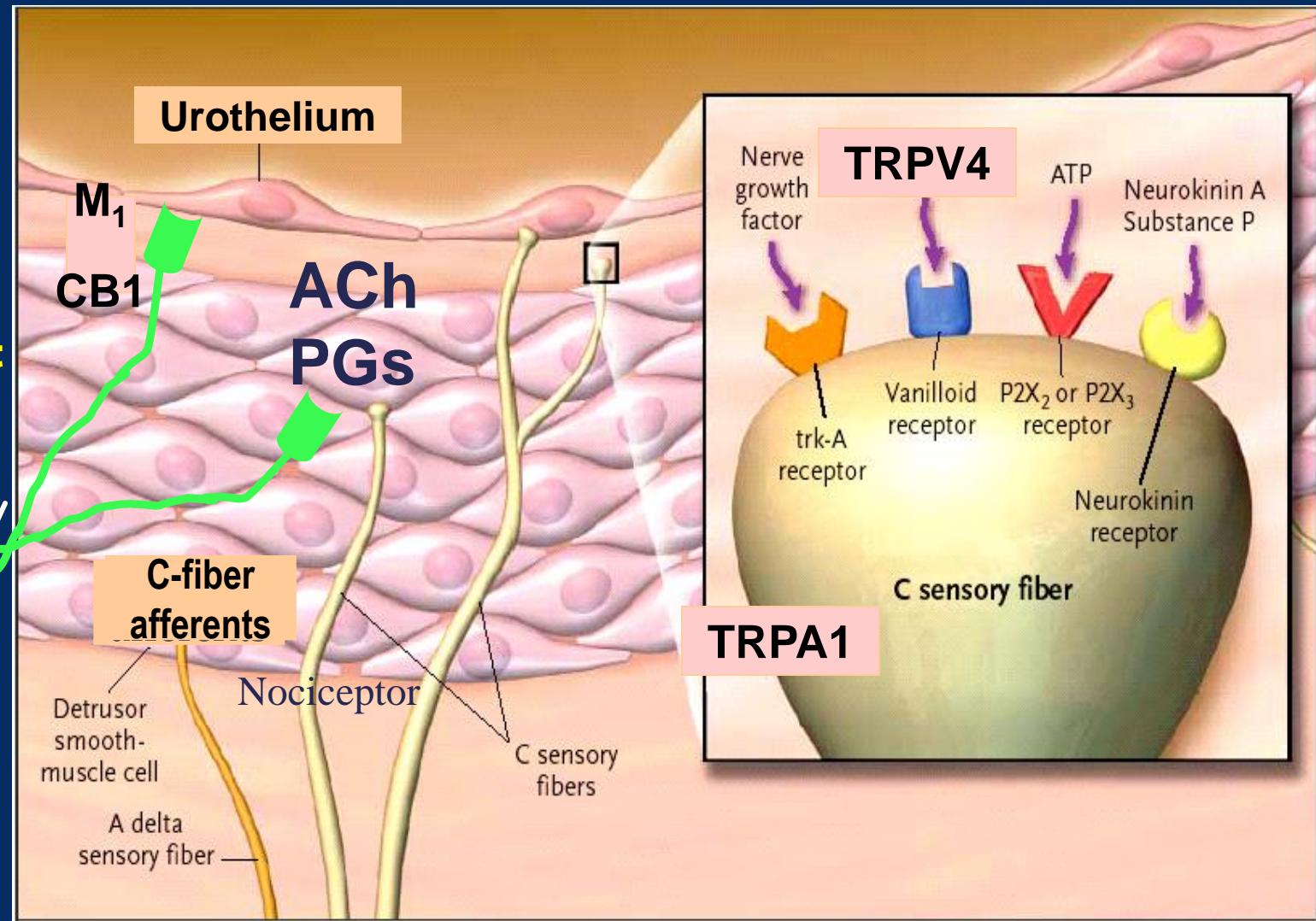
# Therapeutic targets



- Mucosal (Afferent) signaling  
and/or
- Myocyte (Efferent) signaling
- Supraspinal and spinal centers

**Bladder filling**

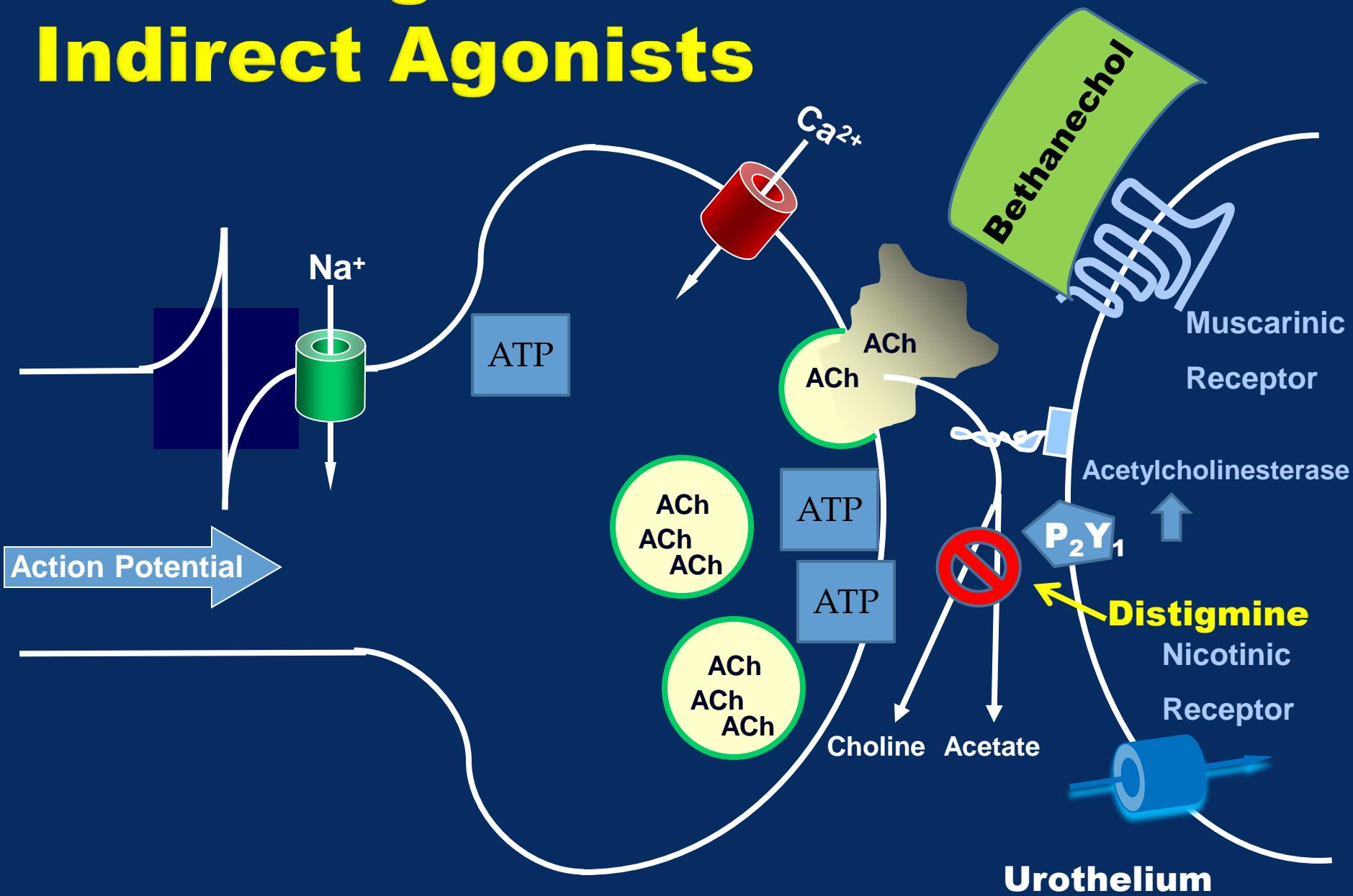
# Mucosal Signaling- Targets



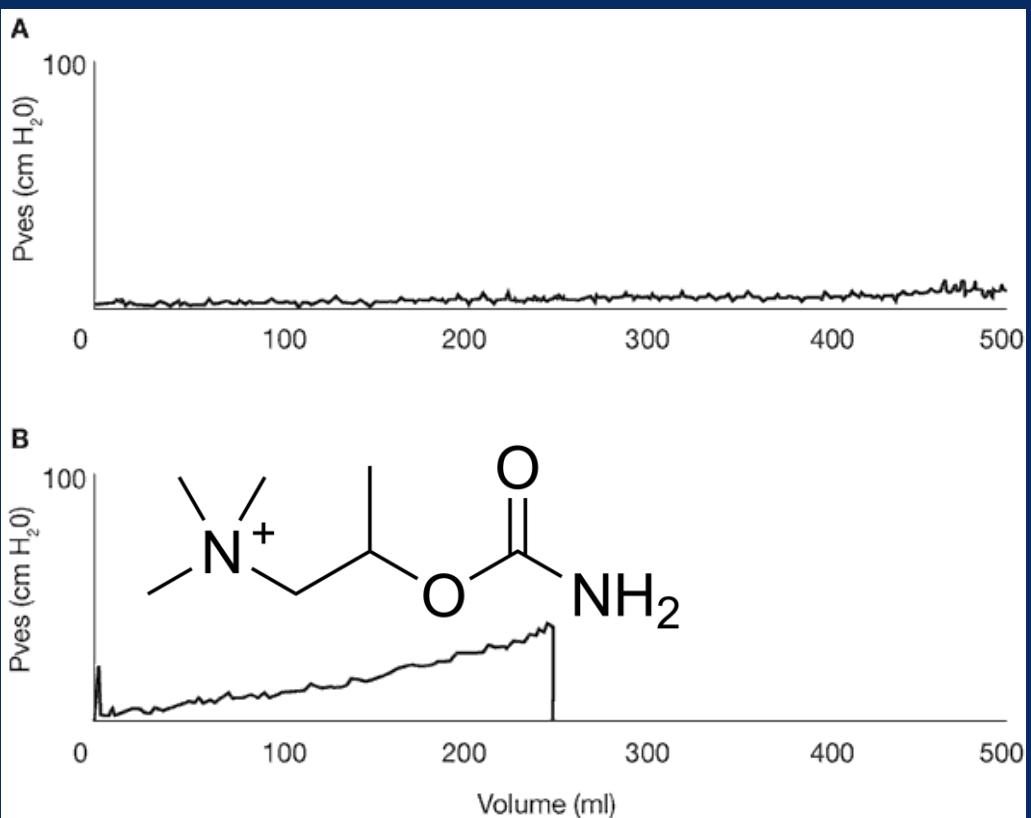
# Potential Targets

- Acetylcholine - direct or indirect cholinergics
- Prostaglandin E2 – EP2/EP3 dual agonists
- Neurite growth Enhancers- TAC302, Amitriptyline
- TRP channels - TRPV4, TRPA1, TRPM8 partial or complete agonists
- ATP - P<sub>2</sub>Y<sub>1</sub> receptor antagonists

# Cholinergic Deficit- Direct vs Indirect Agonists

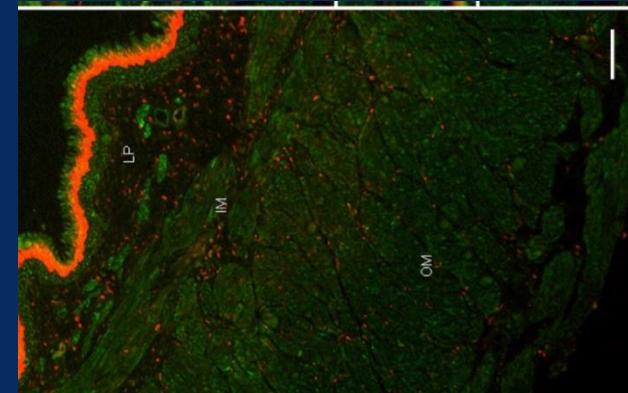
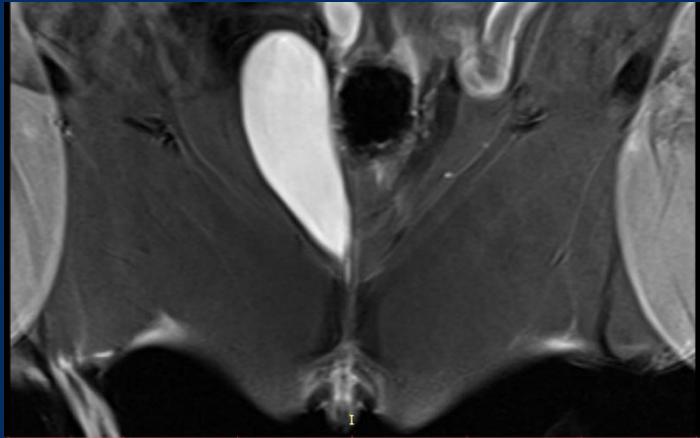


# Bethanechol & UAB



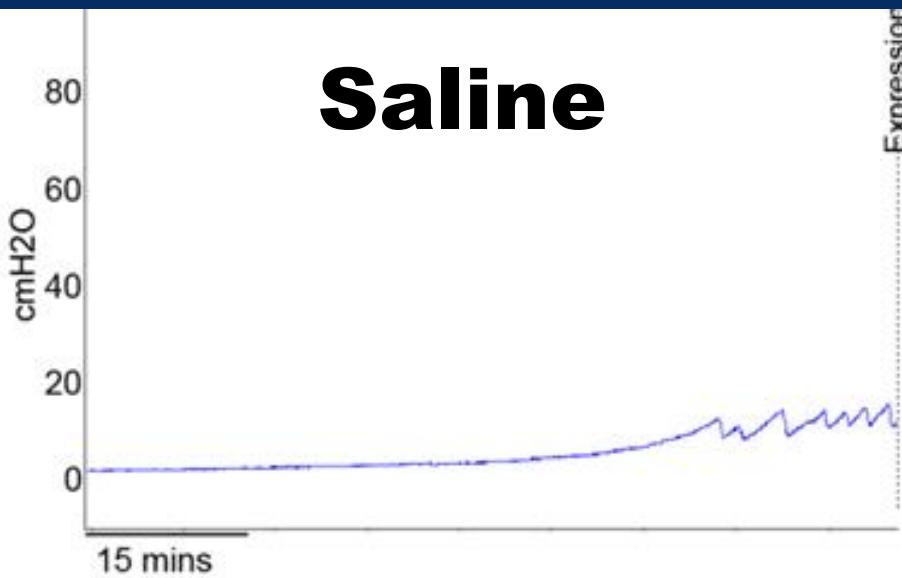
- Baseline CMG - in Diabetic UAB before drug
- CMG 30 minutes after 25 mg bethanechol
- Pdet Qmax 35 cm H<sub>2</sub>O at a volume of 250 ml
- Level of evidence 4; Grade of recommendation D

# Intravesical PGE2 For Atonic Bladder

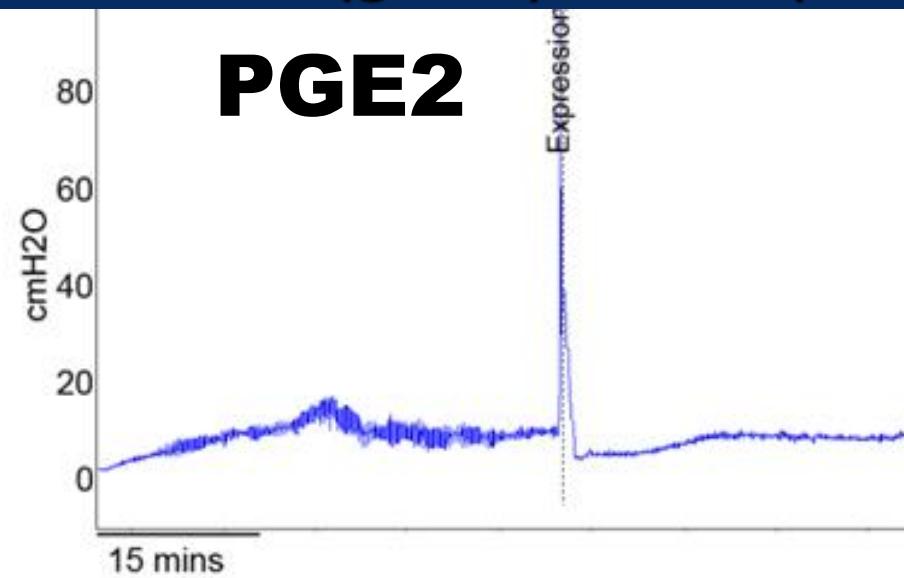


EP1 (green) Cox-1 (red)

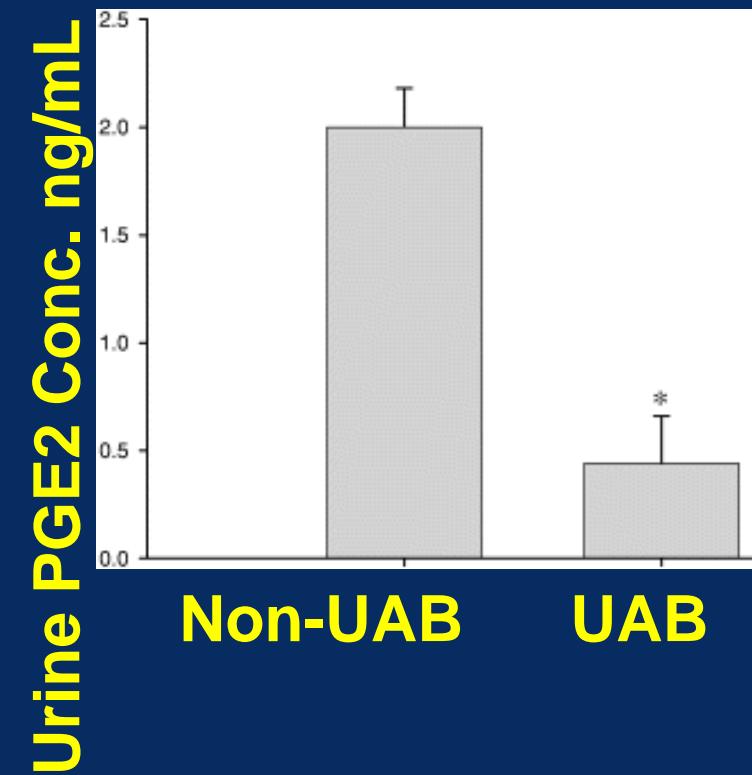
**Saline**



**PGE2**

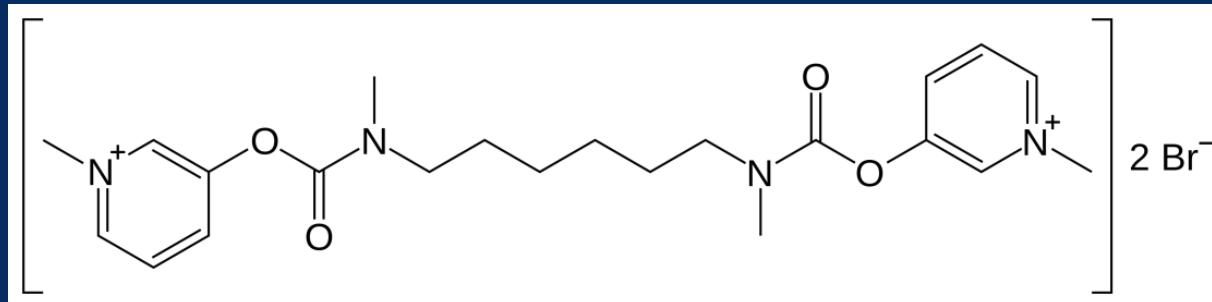


# Bethanechol + PGE2



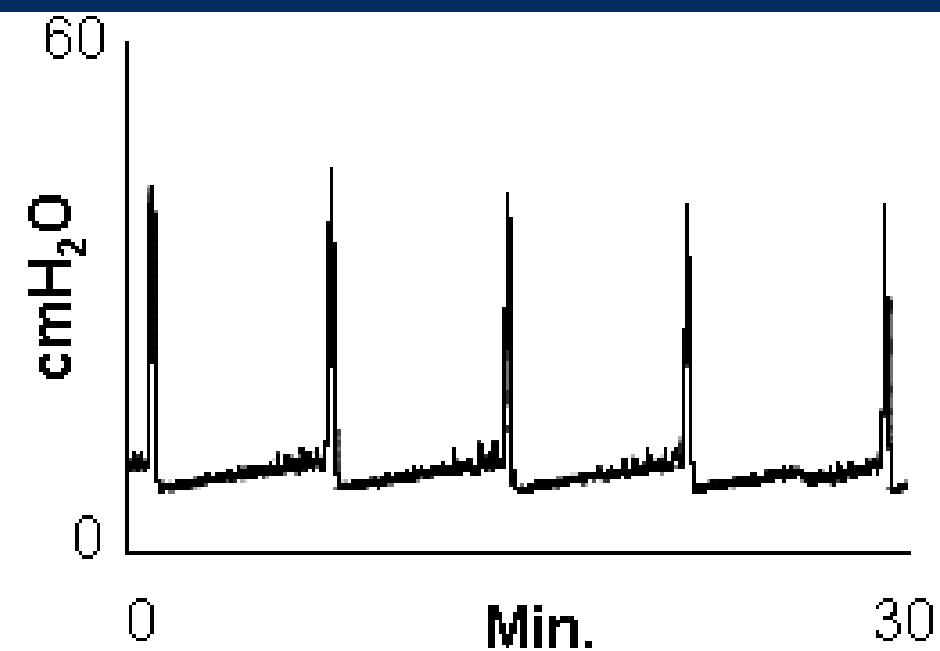
- Bethanechol 50 mg q.i.d, for 6 weeks + weekly intravesical PGE2 (1.5 mg/20 mL) to 9 male UAB
- PVR at 3 months decreased from 426 (405–480) to 325 (290–252) mL
- Limited therapeutic effect over placebo

# Distigmine & UAB

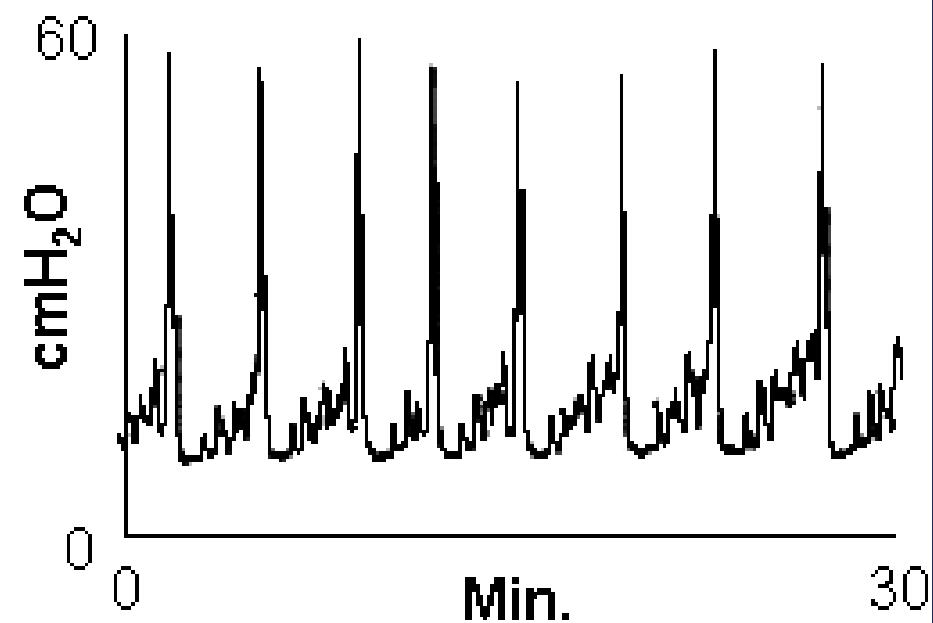


- Distigmine 5 mg daily add-on to α1-blockers for 8 weeks in 18 ♂ and 21 ♀ UAB patients
- Ave. age 75 y and baseline PVR ≥ 50mL
- Significant reduction of PVR and IPSS
- Frequent defecation, fecal incontinence, diarrhea, frequent urination in 4 subjects
- Level of evidence 4; Grade of recommendation D

# Intravesical Administration- Direct Agonist

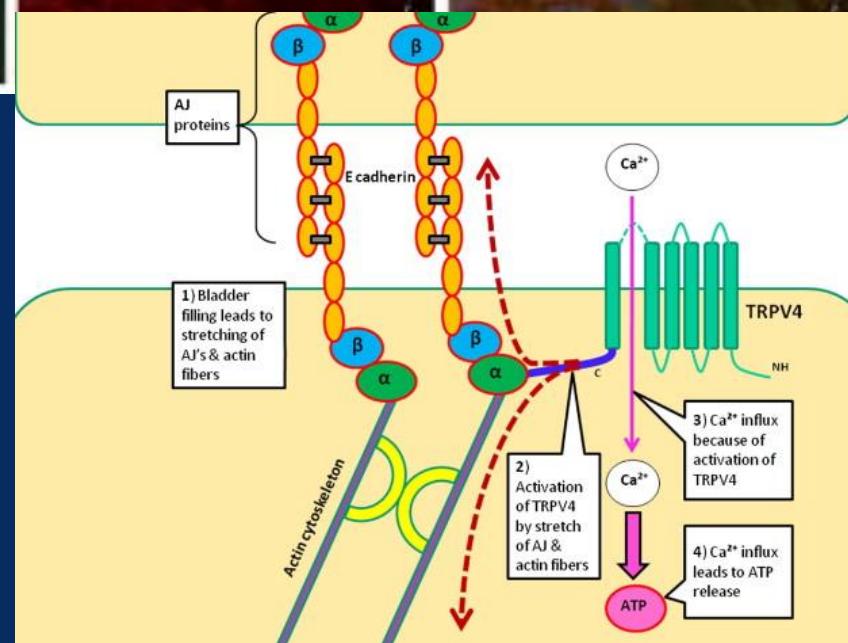
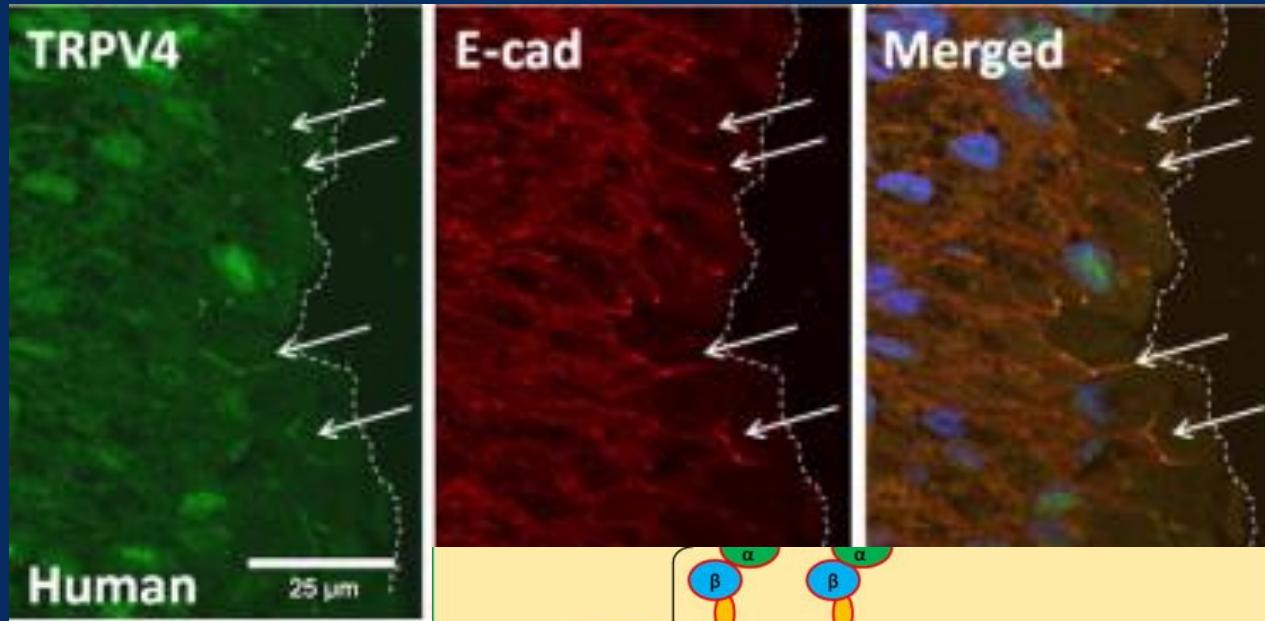
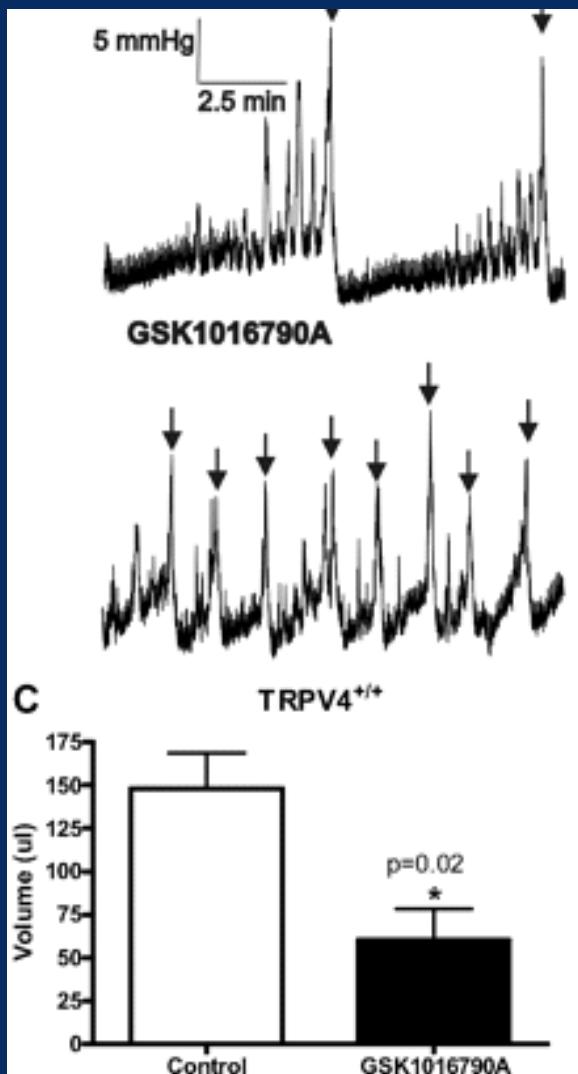


Intravesical  
saline

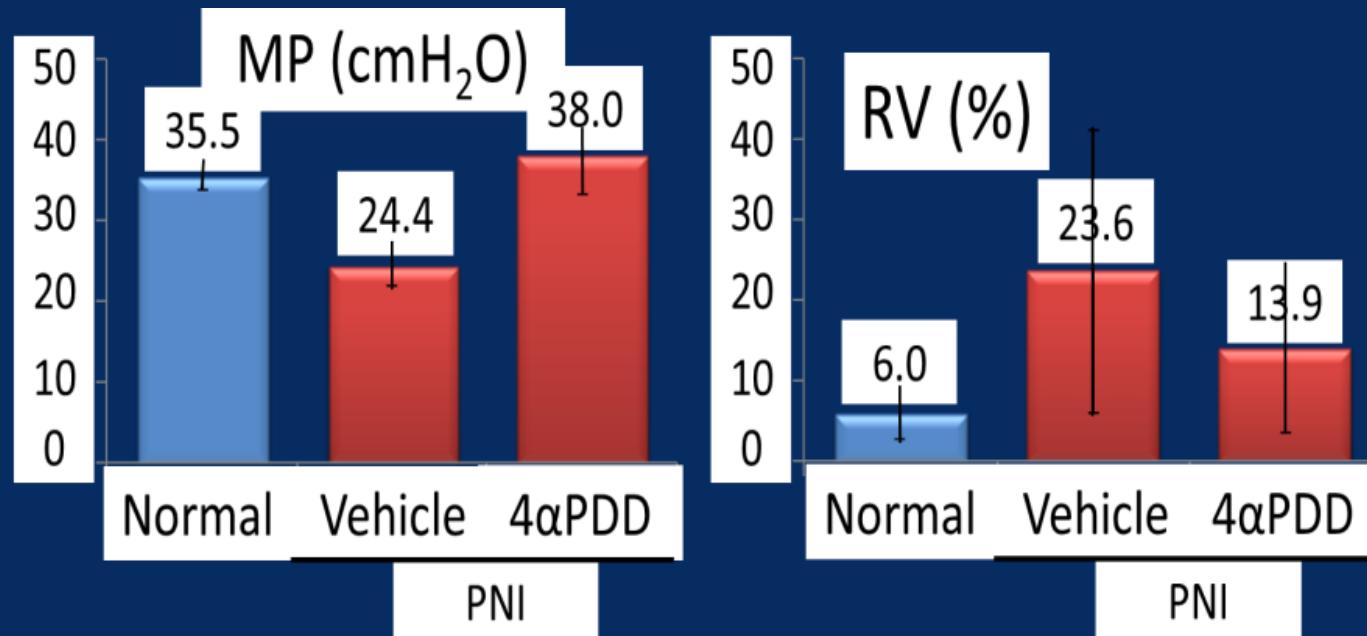
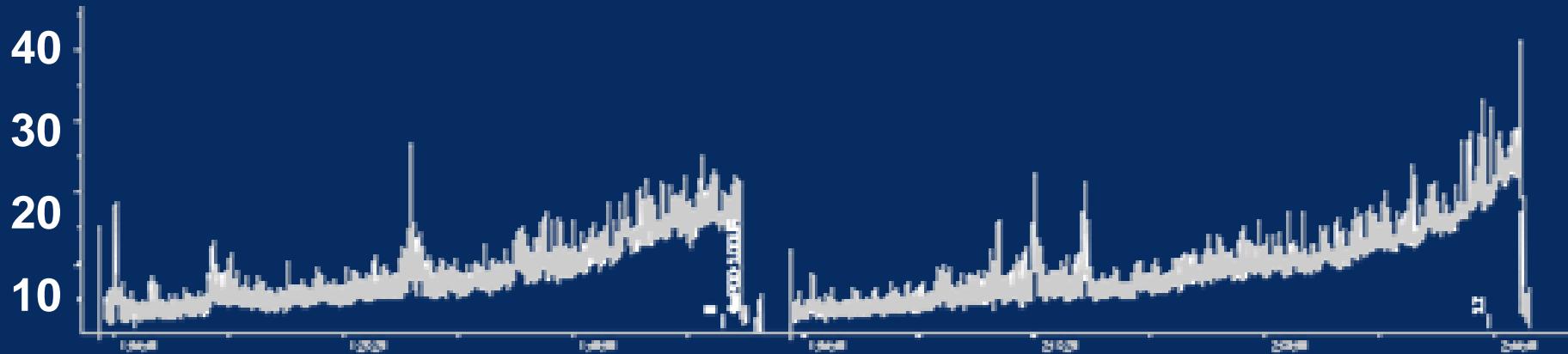


Intravesical  
Carbachol 30uM

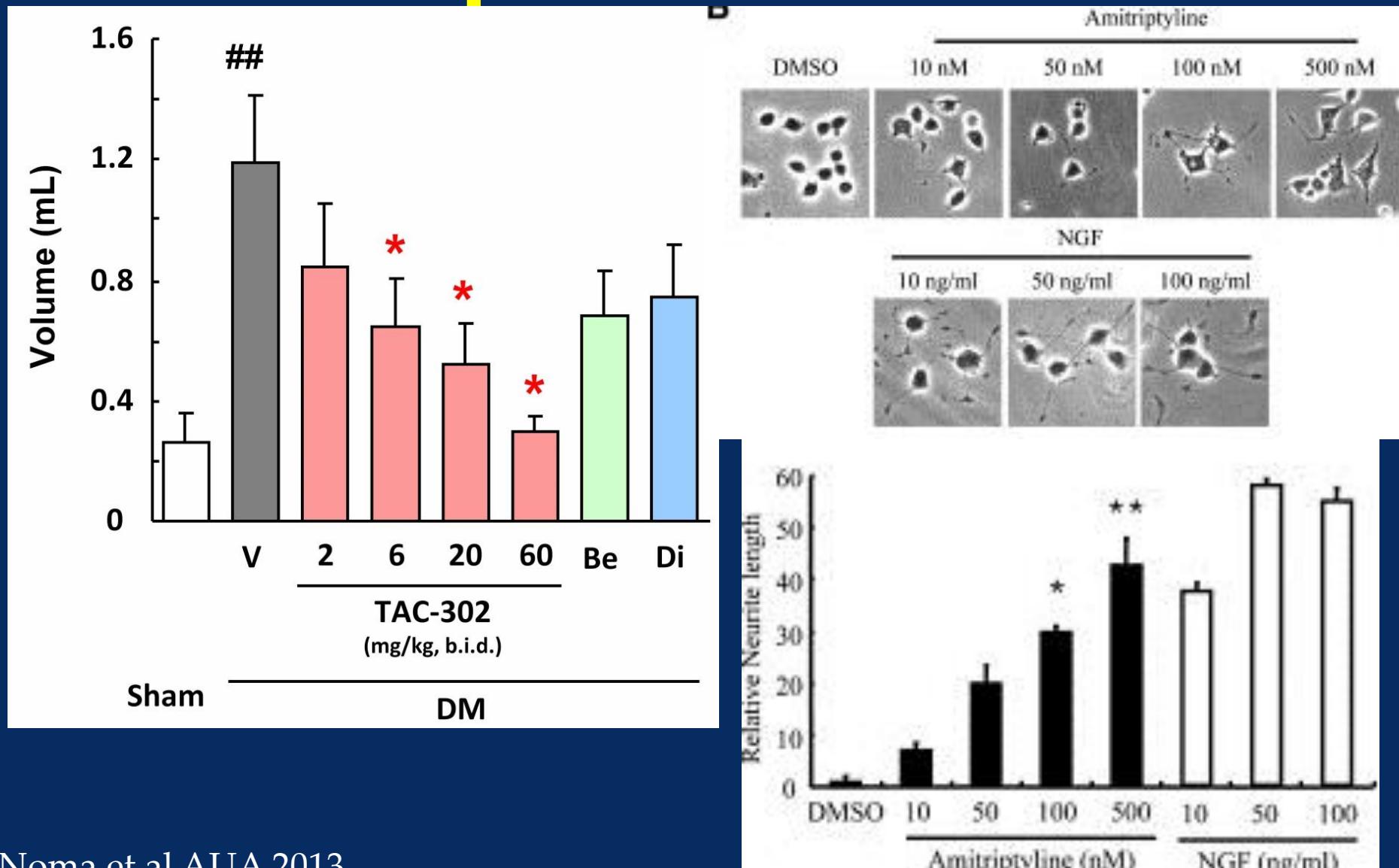
# Mechanoreceptor-TRPV4



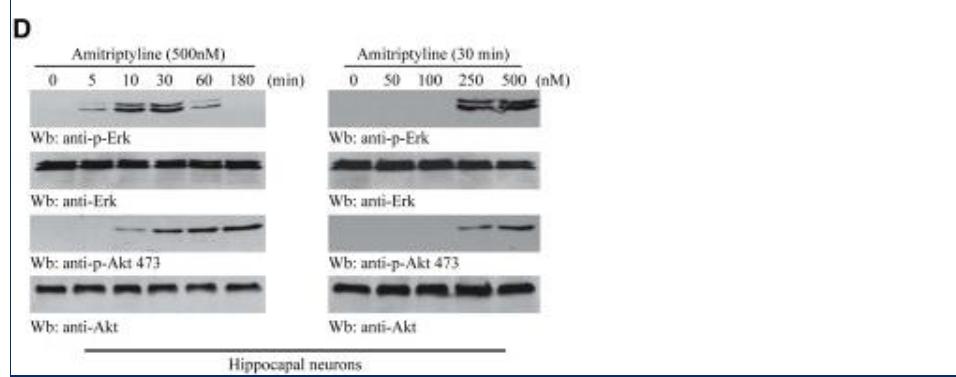
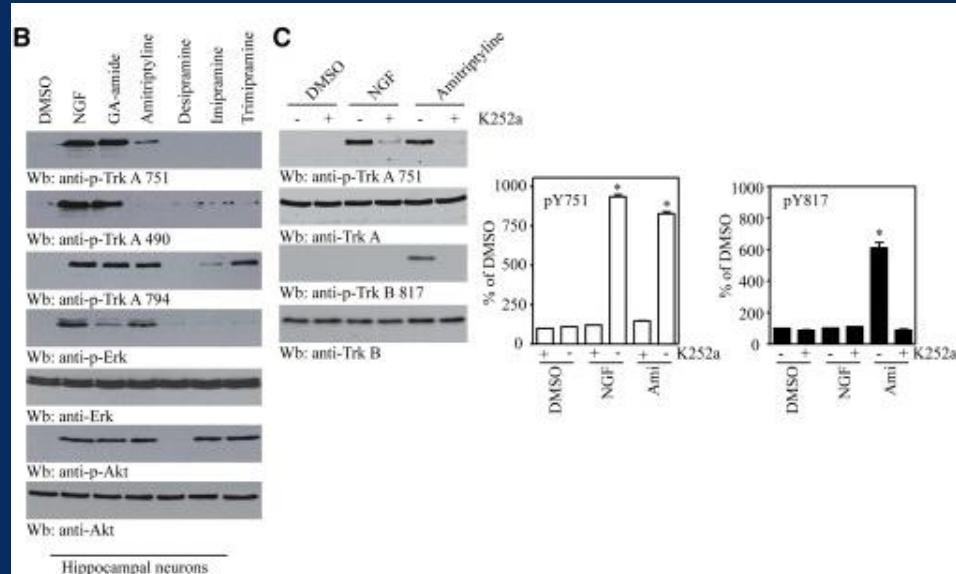
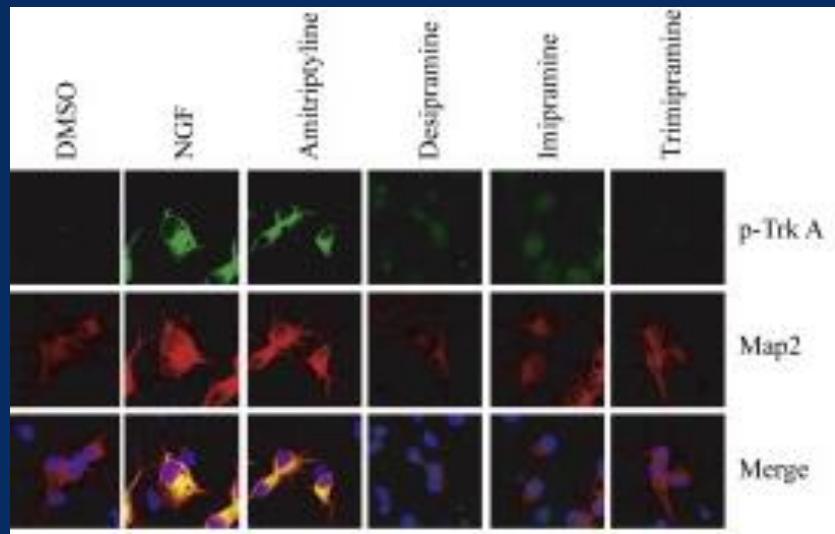
# TRPV4 and UAB model



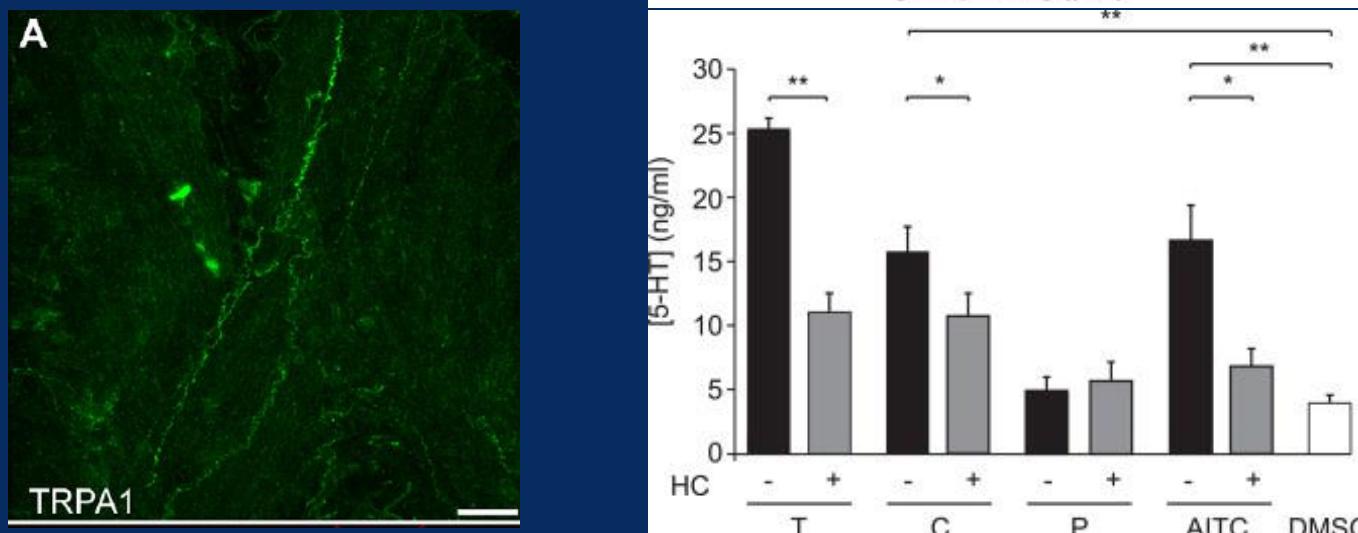
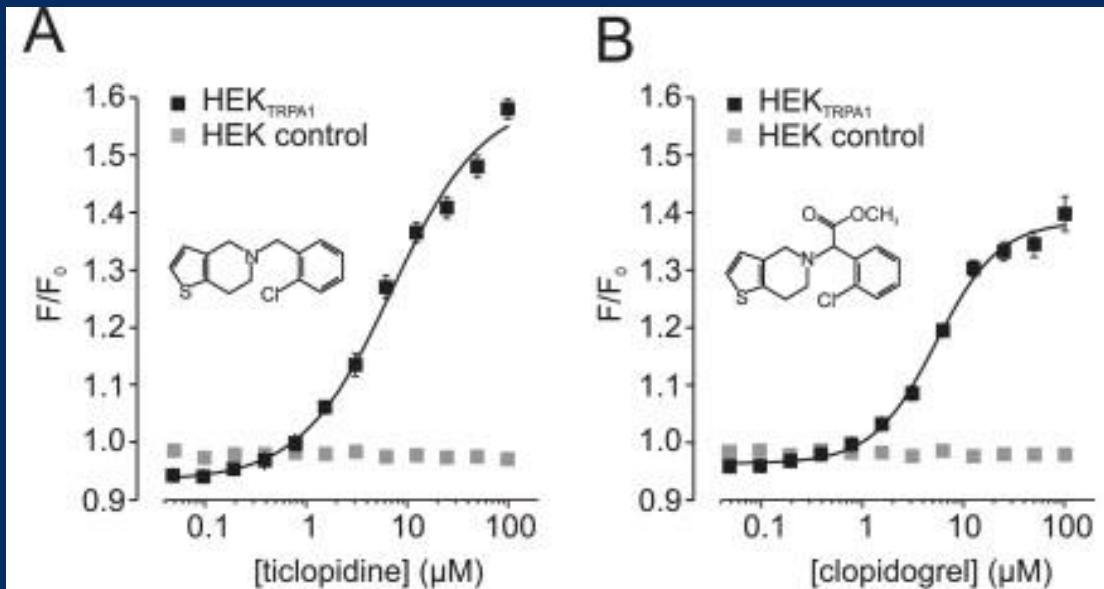
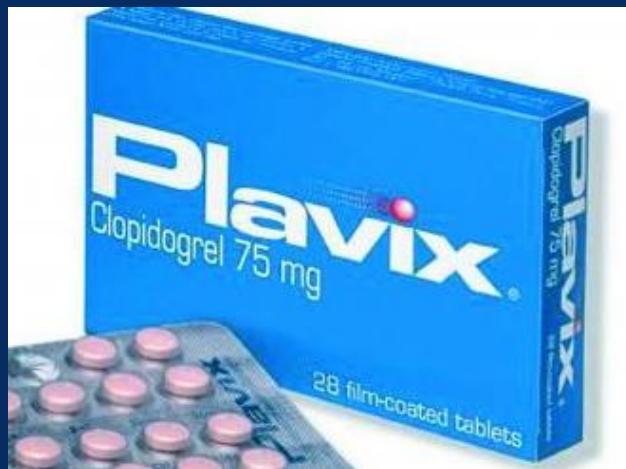
# Neurotrophin Mimetics



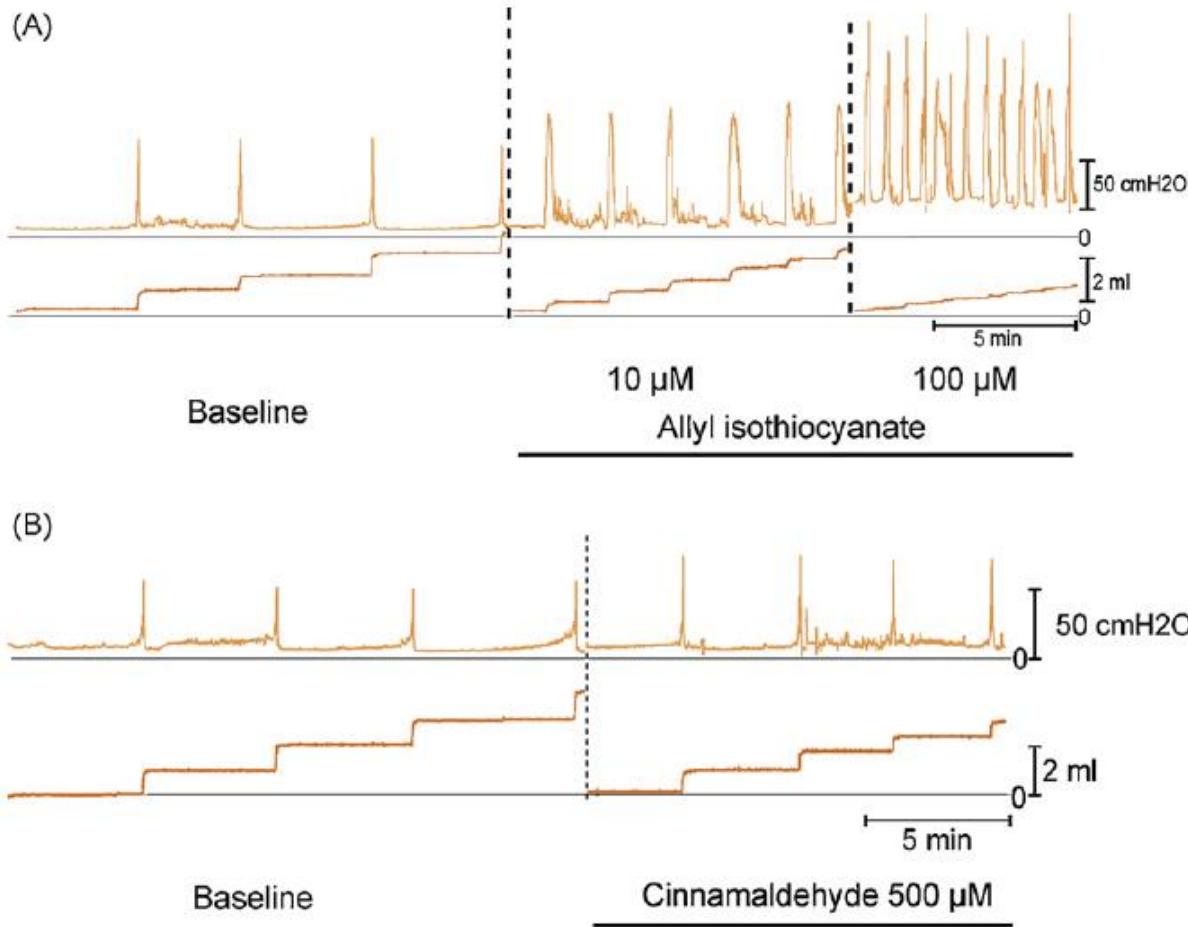
# NGF Mimetic- Amitriptyline



# Plavix & TRPA1



# TRPA1 Agonists- Intravesical

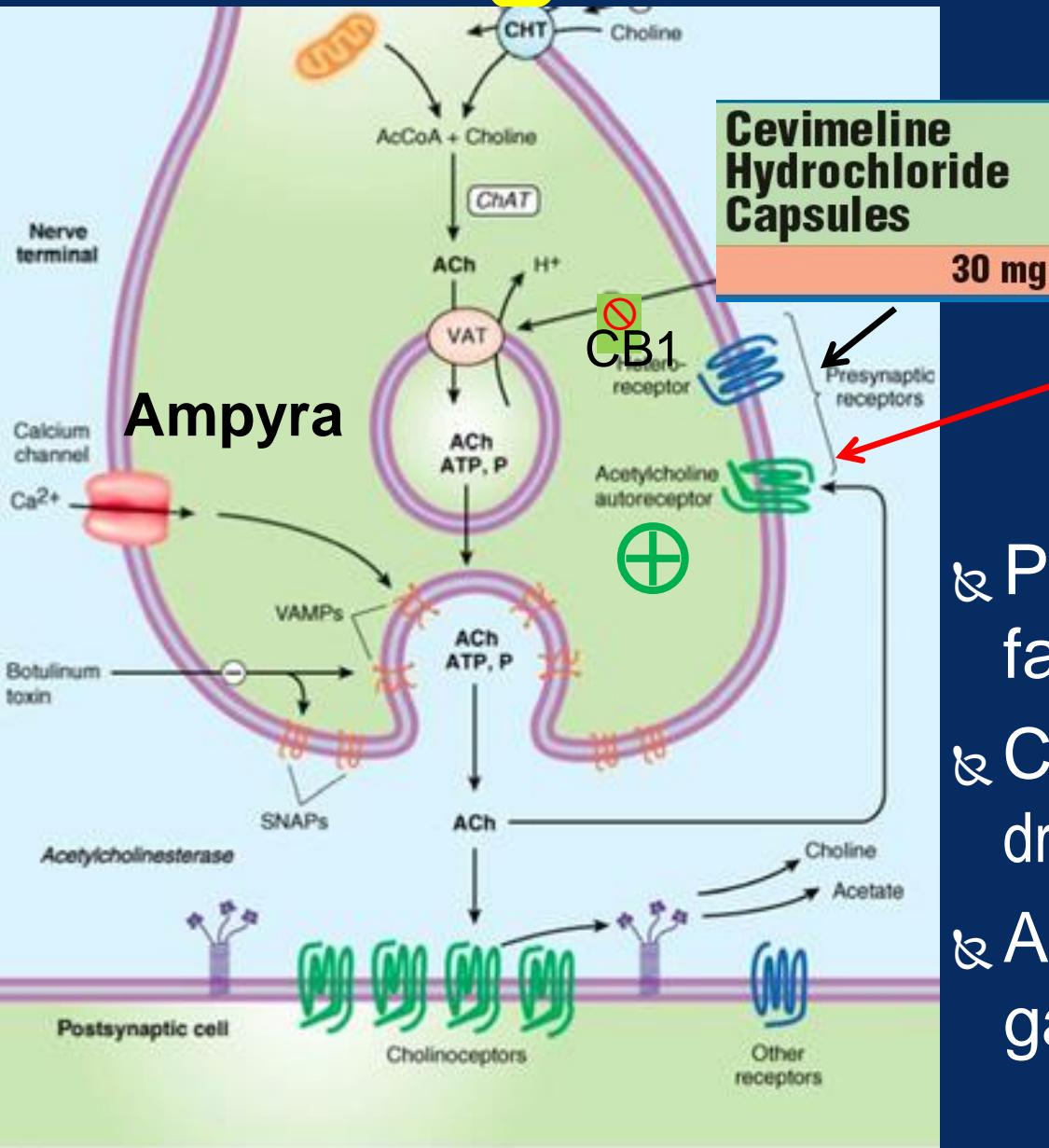


# Myocyte signaling- Target



- Facilitate Neurogenic contraction
  - M<sub>1</sub> muscarinic agonists,
  - N-type VGCC agonist (Ampyra)
  - CB<sub>1</sub> antagonists
- Facilitate Spontaneous Contraction-
  - KCNQ and HCN channel blockers
- Decrease outlet Resistance
  - α<sub>1</sub> AR antagonists,
  - NO donors, PDE9 inhibitors, BoNT-A,
  - benzodiazepines, Baclofen, Dantrolene

# Neurogenic Contraction



Cevimeline  
Hydrochloride  
Capsules

30 mg

100錠 (10錠×10)

機能性ディスペプシア(FD)治療剤

アコファイド錠100mg  
Acofide® Tablets 100mg

成分: 1錠中アコチアミド塩酸塩水和物100mg含有  
注意—医師等の処方せんにより使用すること

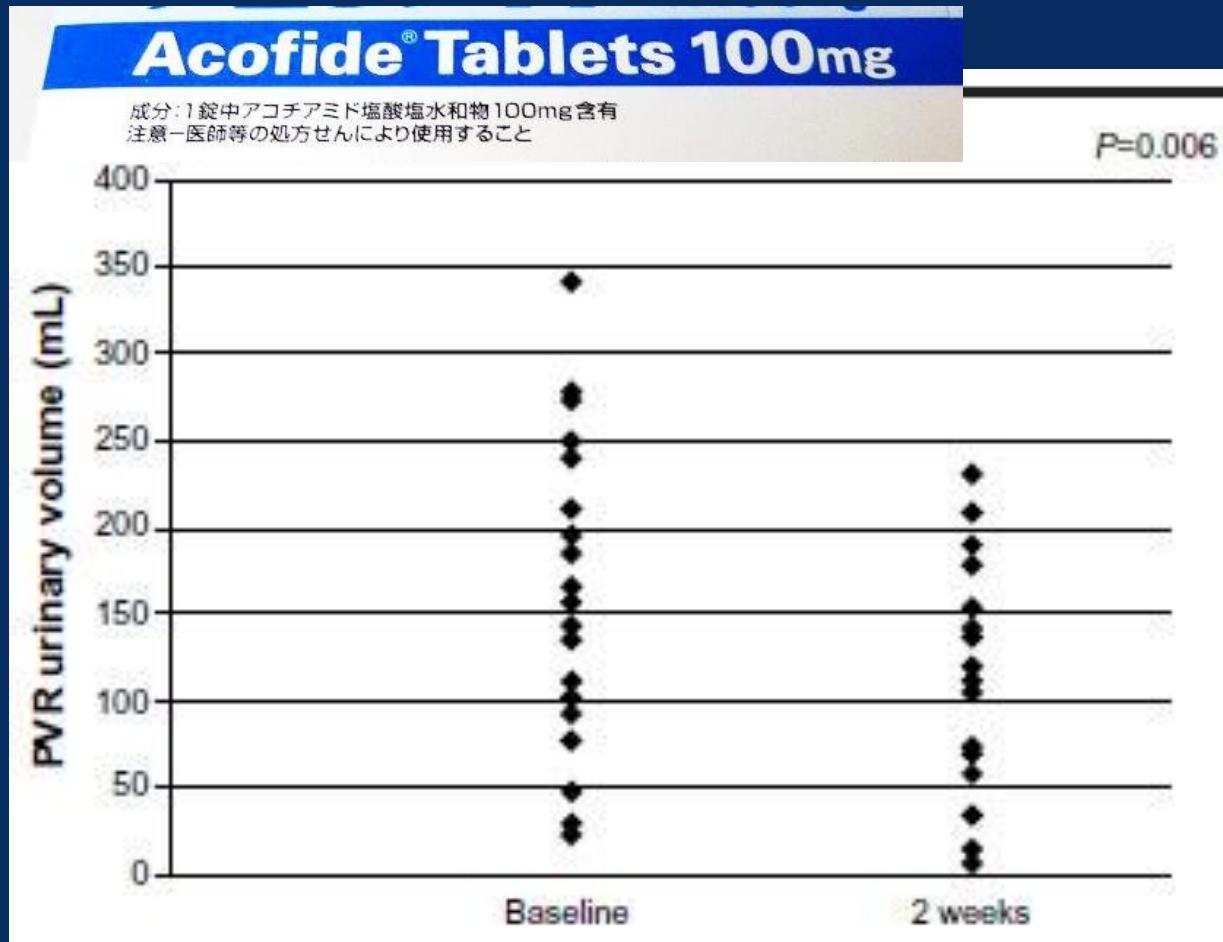
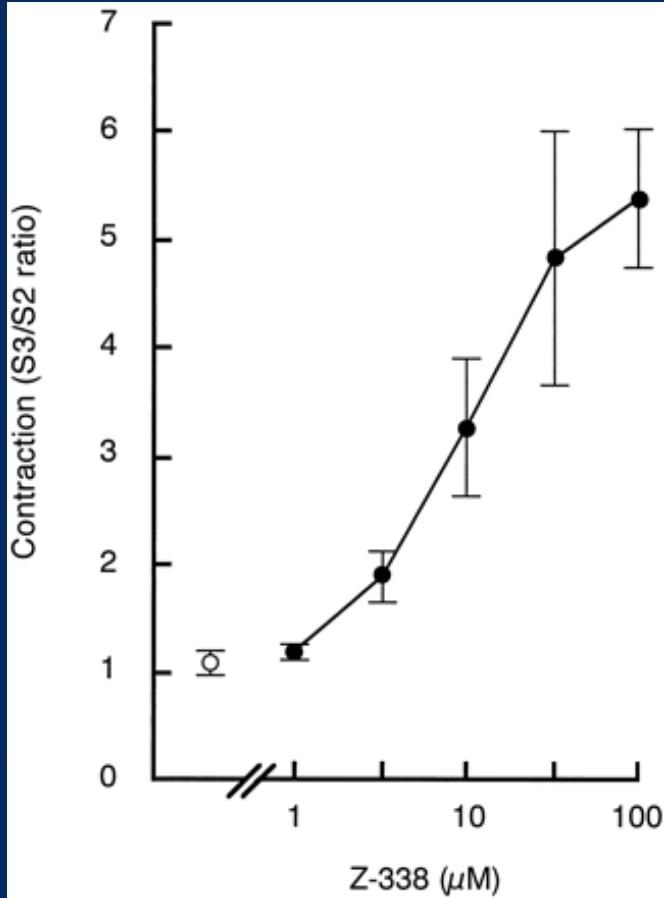
効能・効果、用法・用量、使用上の注意等  
については、添付文書をご覧ください。

製造販売元:  
セリア新薬工業株式会社  
東京都中央区日本橋小舟町10-11

発売元:  
アステラス  
astellas 東京都板橋区

- & Presynaptic M<sub>1</sub> are auto-facilitatory
- & Cevimeline is M<sub>1</sub> agonist (dry mouth drug)
- & Acotiamide is a gastropotokinetic agent

# Acotiamide – Reduces PVR

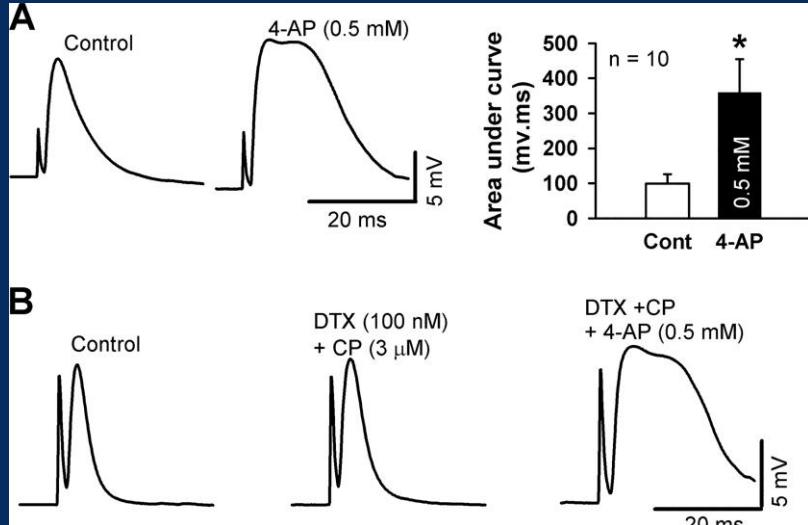
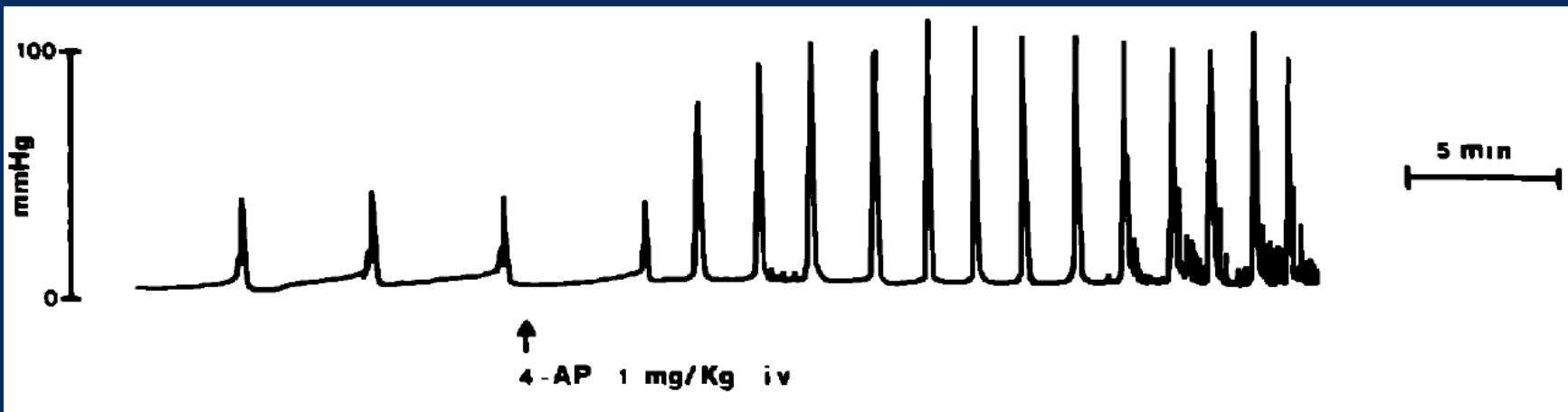


GP Stomach Strips

Res Rep Urol. 2015 8;7:81-3.

J Pharmacol Exp Ther. 2000;294(1):33-7.

# Neurogenic Contraction



- 4-AP, (Ampyra ) potentiate voiding
- Directly stimulate pre-synaptic N-type VGCC (0.5mM) and blocks Kv1 family at 1mM
- Fampridine 30mg daily dose improved spasticity in SCI

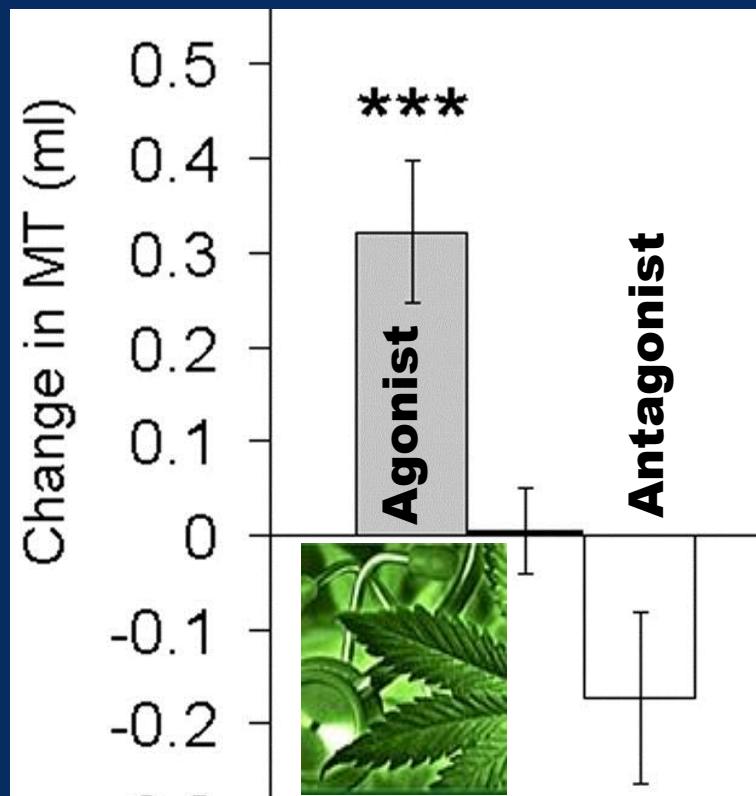
Maggi et al. Brain Res. 1988 May 24;449(1-2):61-70.

Wu Z et al. J. Biol. Chem. 2009;284:36453-36461

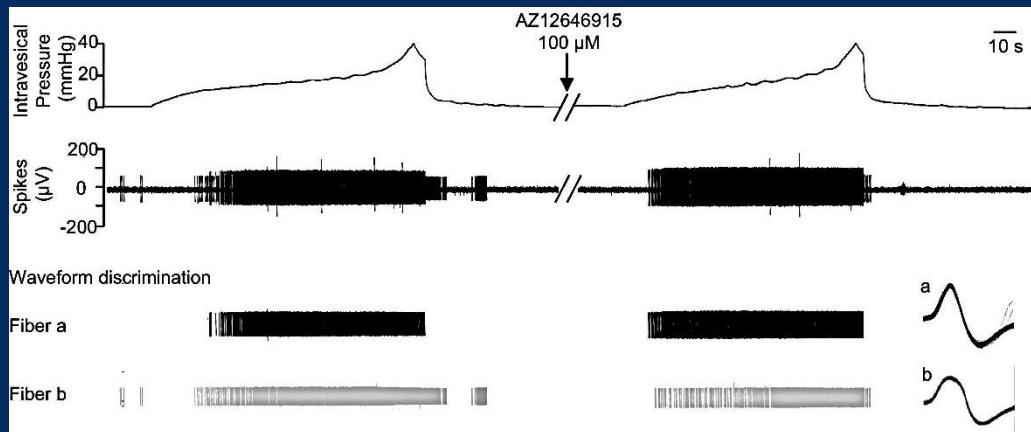
Arch Med Res. 2010;41(7):567-75.

Spinal Cord. 2013 Nov 12

# **CB<sub>1</sub> Antagonist & Afferents**

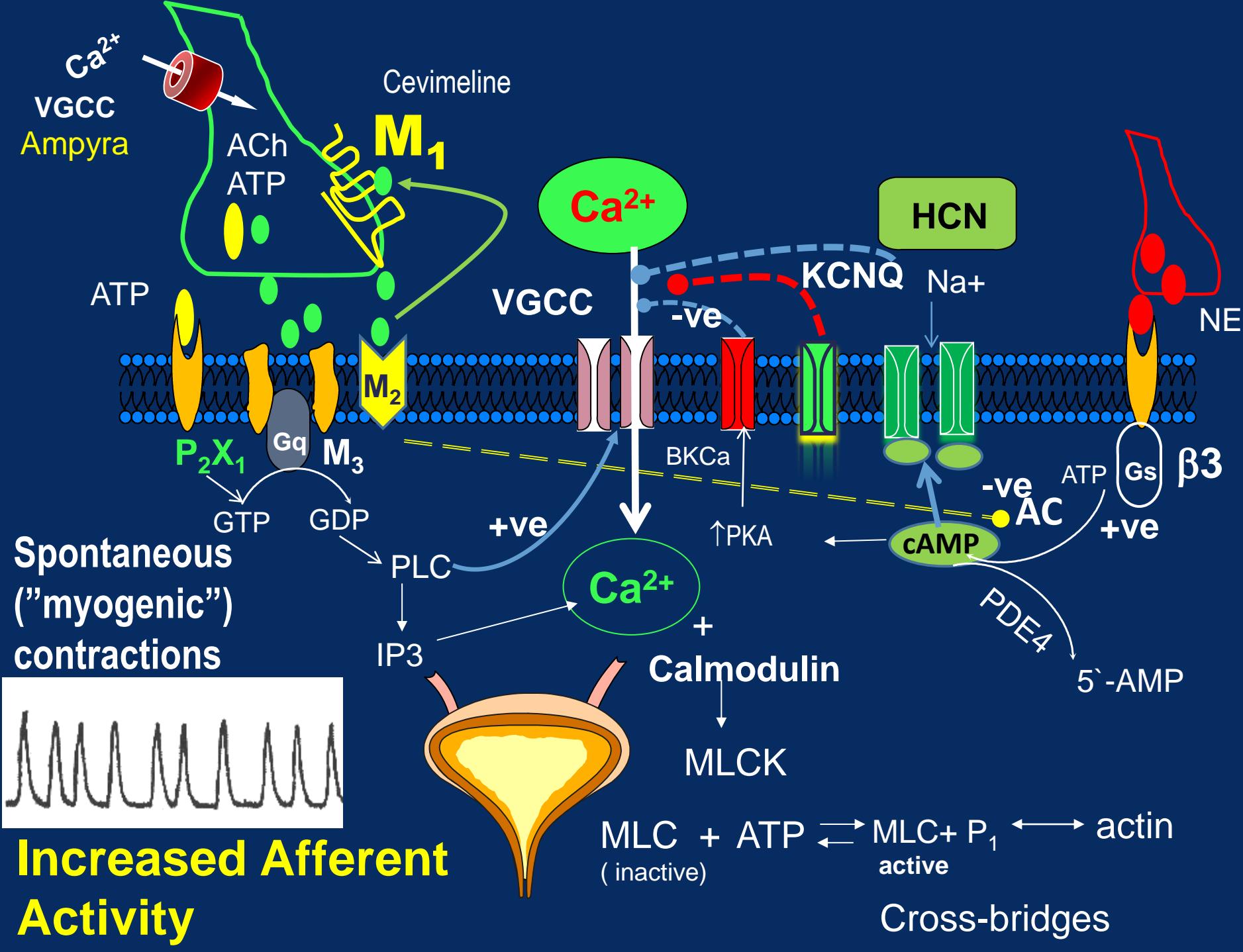


CB<sub>1</sub> agonist raised MT and  
CB<sub>1</sub> antagonist reduced MT

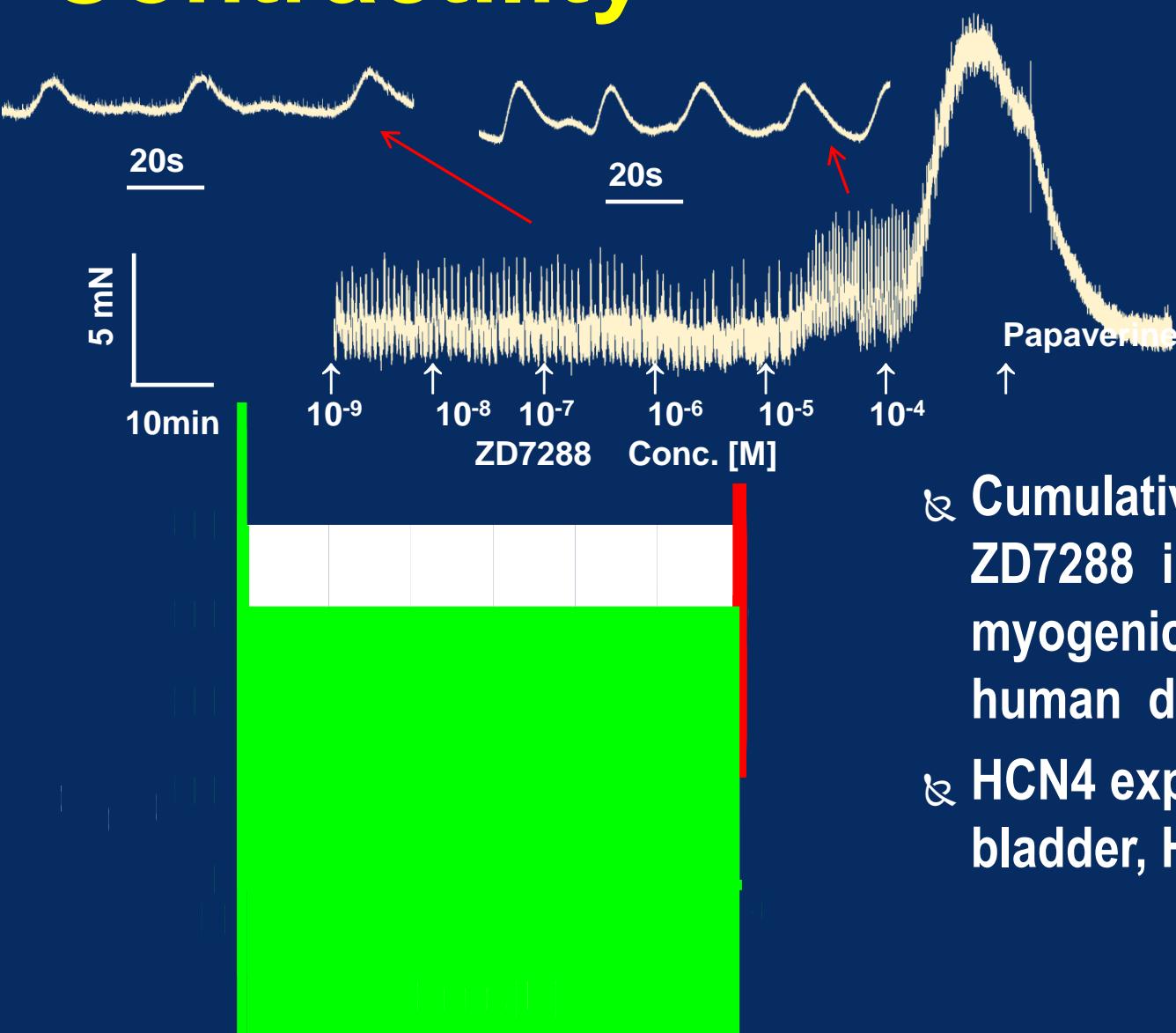


- CB<sub>1</sub> agonist reduced activity in high threshold afferents
- Can anti-obesity drug Rimonabant increase afferent input in UAB?

Dmitrieva et al. J. Neurosci. 2002;22:7147-7153  
Walczak et al. Neuroscience 2009;159(3):1154-63.  
Exp Clin Endocrinol Diabetes 2013;121(1):20



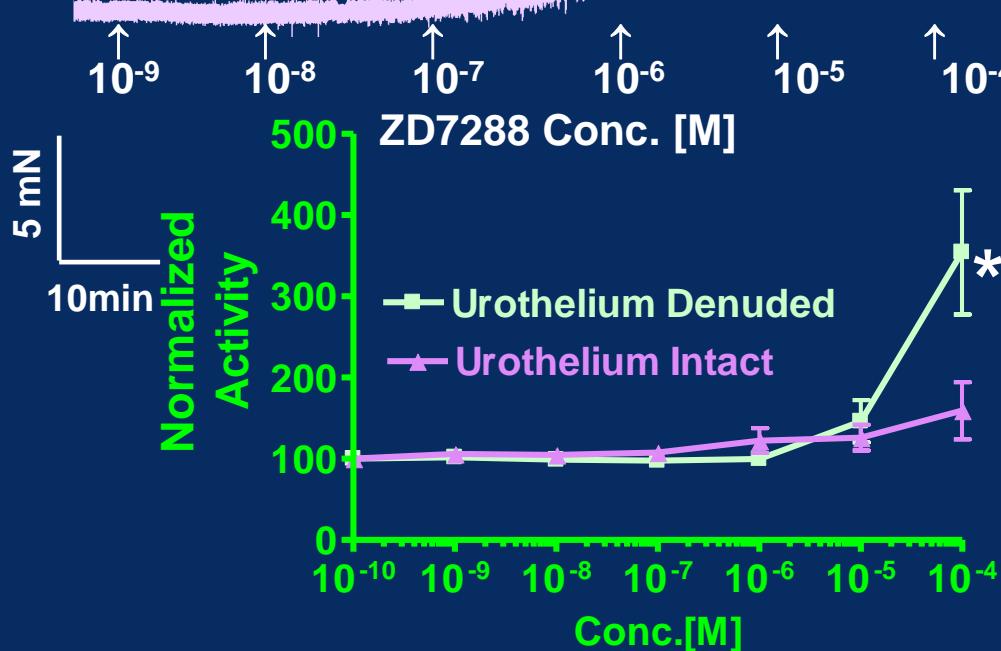
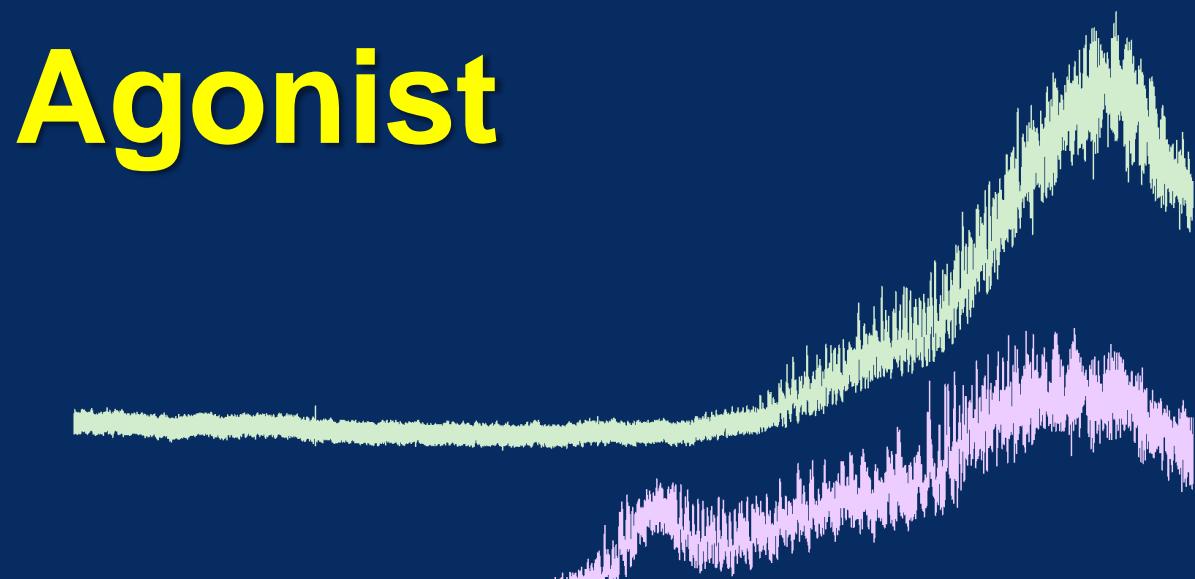
# HCN Blockade – Bladder Contractility



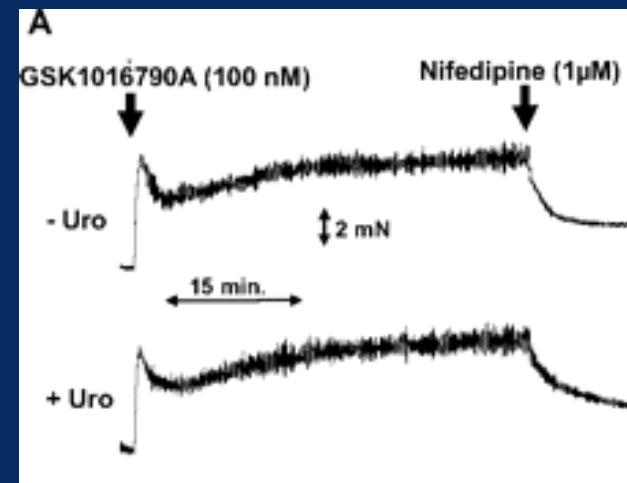
- ¶ Cumulative addition of ZD7288 increased the myogenic contractility of human detrusor strips
- ¶ HCN4 expressed in human bladder, HCN2 in heart

# HCN Blocker vs TRPV4 Agonist

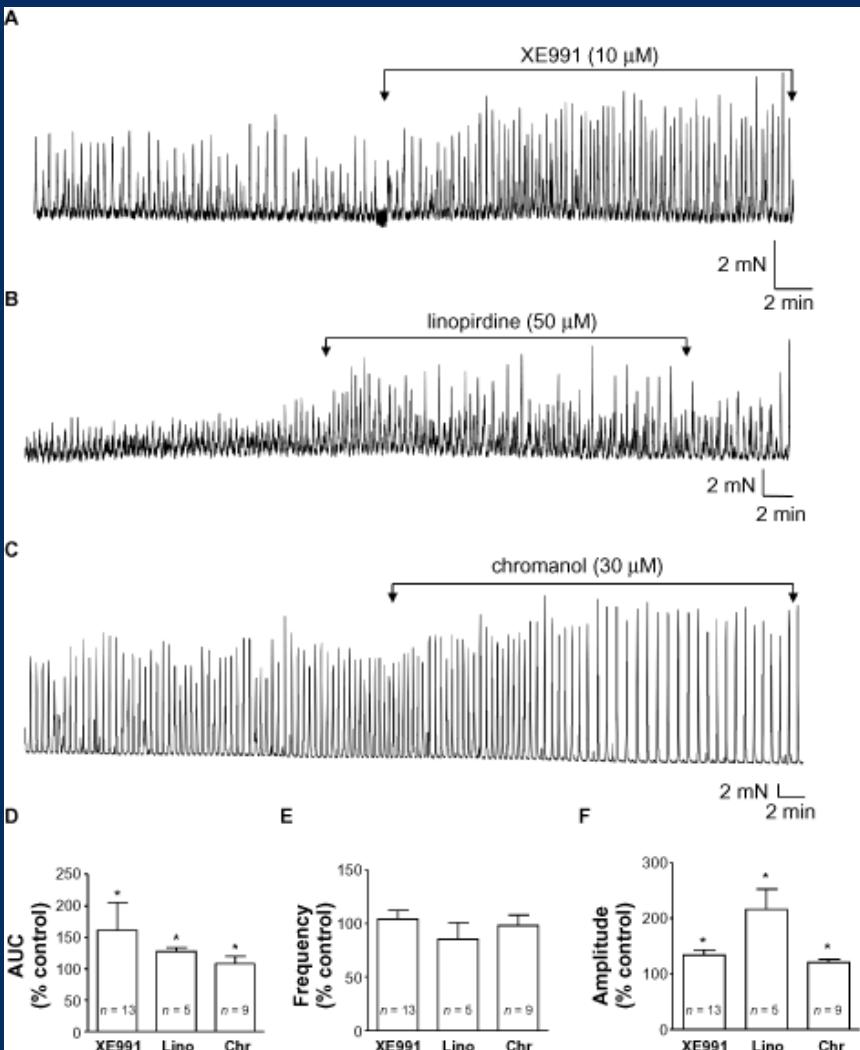
Urothelium denuded



Urothelium Intact



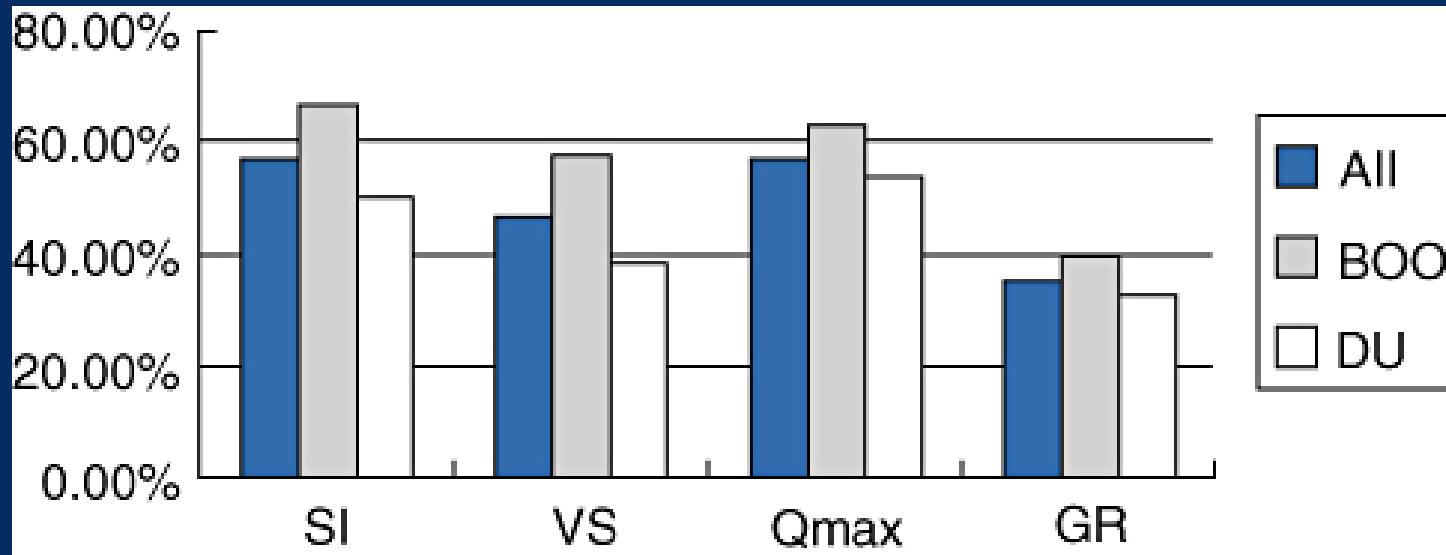
# KCNQ Blocker- Spontaneous Contraction



& KCNQ blockers increased TTX resistant contractions of guinea pig detrusor strips

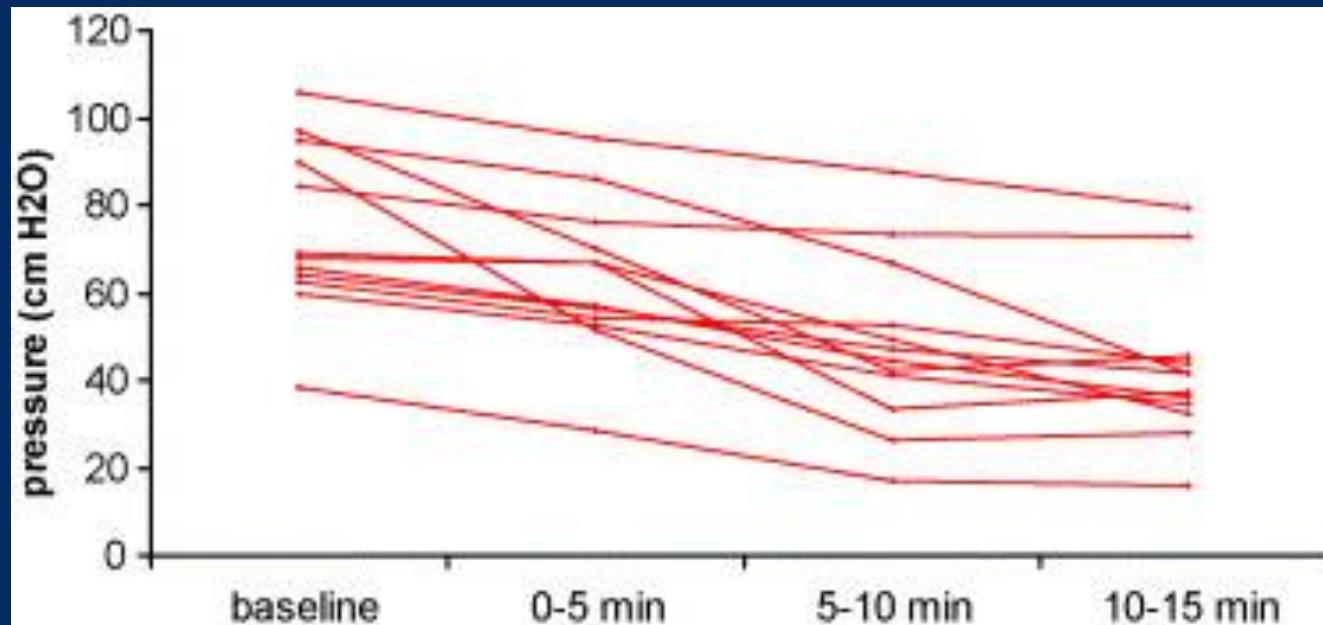
& Frequency and Baseline tone not affected

# Reduction of Outlet Resistance - Tamsulosin



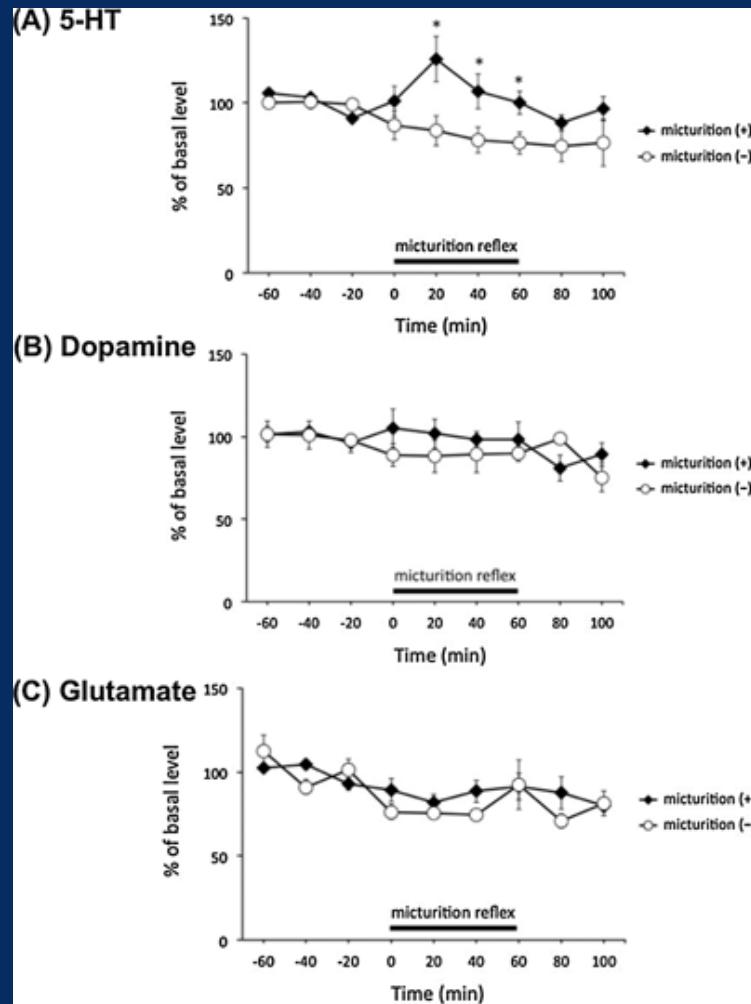
- 97 ♂ with 52 having DU/UAB studied over a 5 year trial
- 0.2 mg Tamsulosin daily for 6 or more weeks
- 32% of DU patients responded to Tamsulosin with >50% reduction in VS combined with >30% increment in Qmax
- Level of evidence 4; Grade of recommendation C**

# Reduction of Urethral Resistance -NO Donors



- Isosorbide dinitrate 10mg sublingually to 12 SCI patients
- Resting external urethral sphincter pressures decreased

# Targeting Spinal & Supraspinal Control



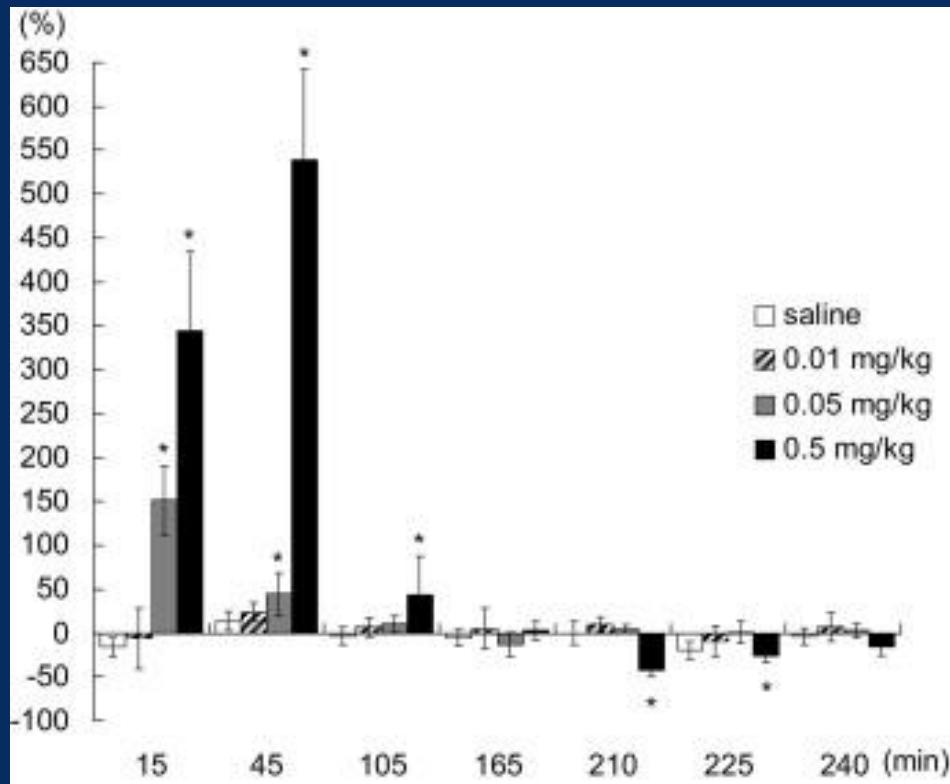
Neurotransmitter levels in rat PFC  
Measured during awake CMG  
by micro dialysis



Laughter is the best medicine because it releases dopamine & 5-HT

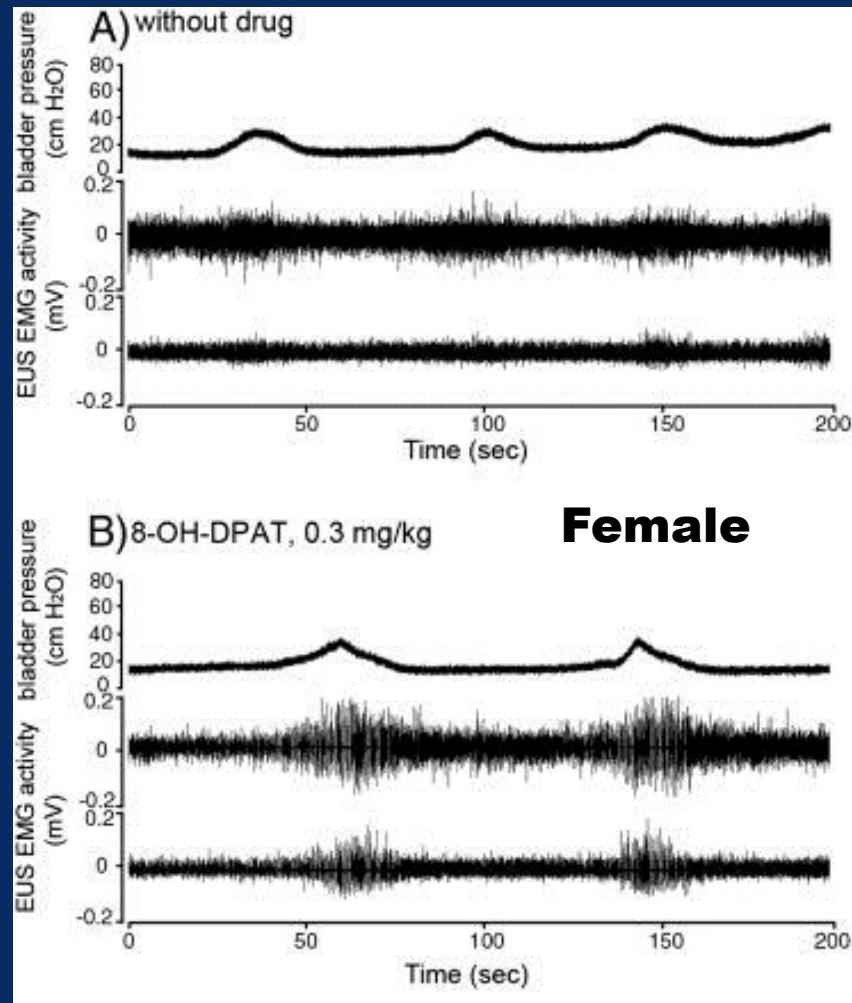
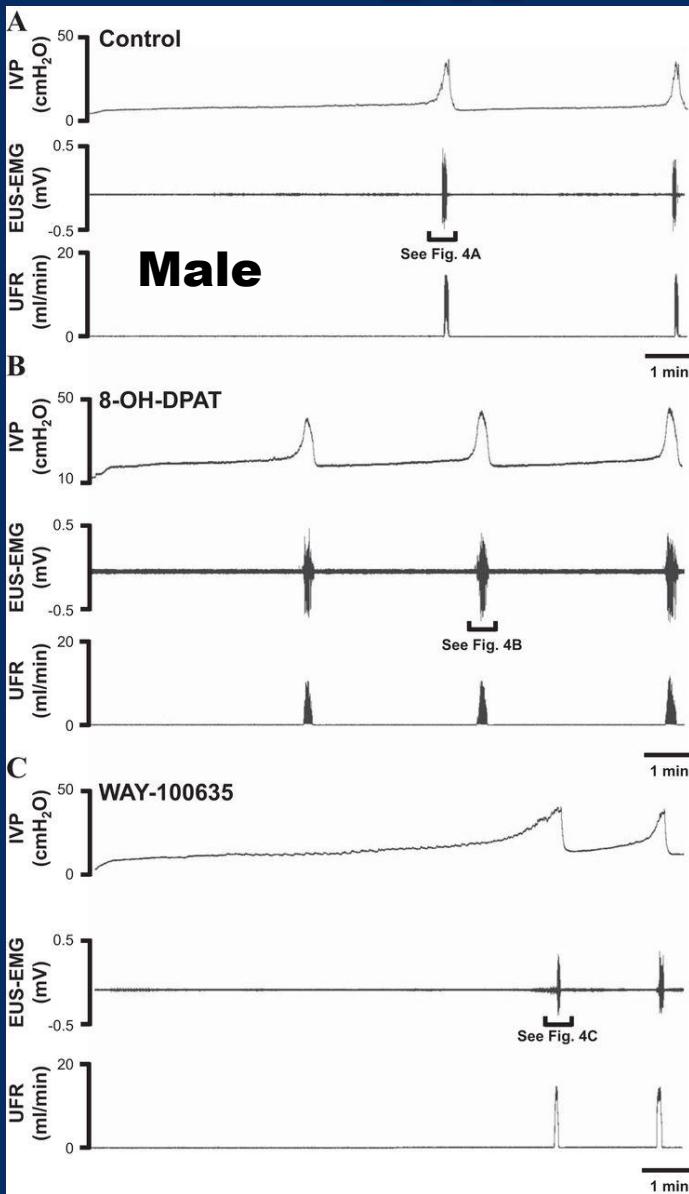
# Apomorphine & Micturition Volume

% change from Baseline



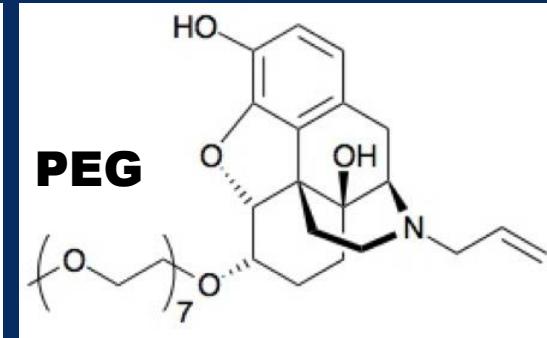
- ❖ Increases voiding frequency and micturition volume upto 45min
- ❖ Apo increases the afferent activity and stimulate central micturition center
- ❖ L-dopa in combination with Domperidone reduced first sensation to void

# 5-HT<sub>1A</sub> Agonist



Exp Neurol 2013;239:210-7.  
Am J Physiol Regul Integr Comp Physiol. 2014  
15;307(10):R1239-50.

# PAMORAs



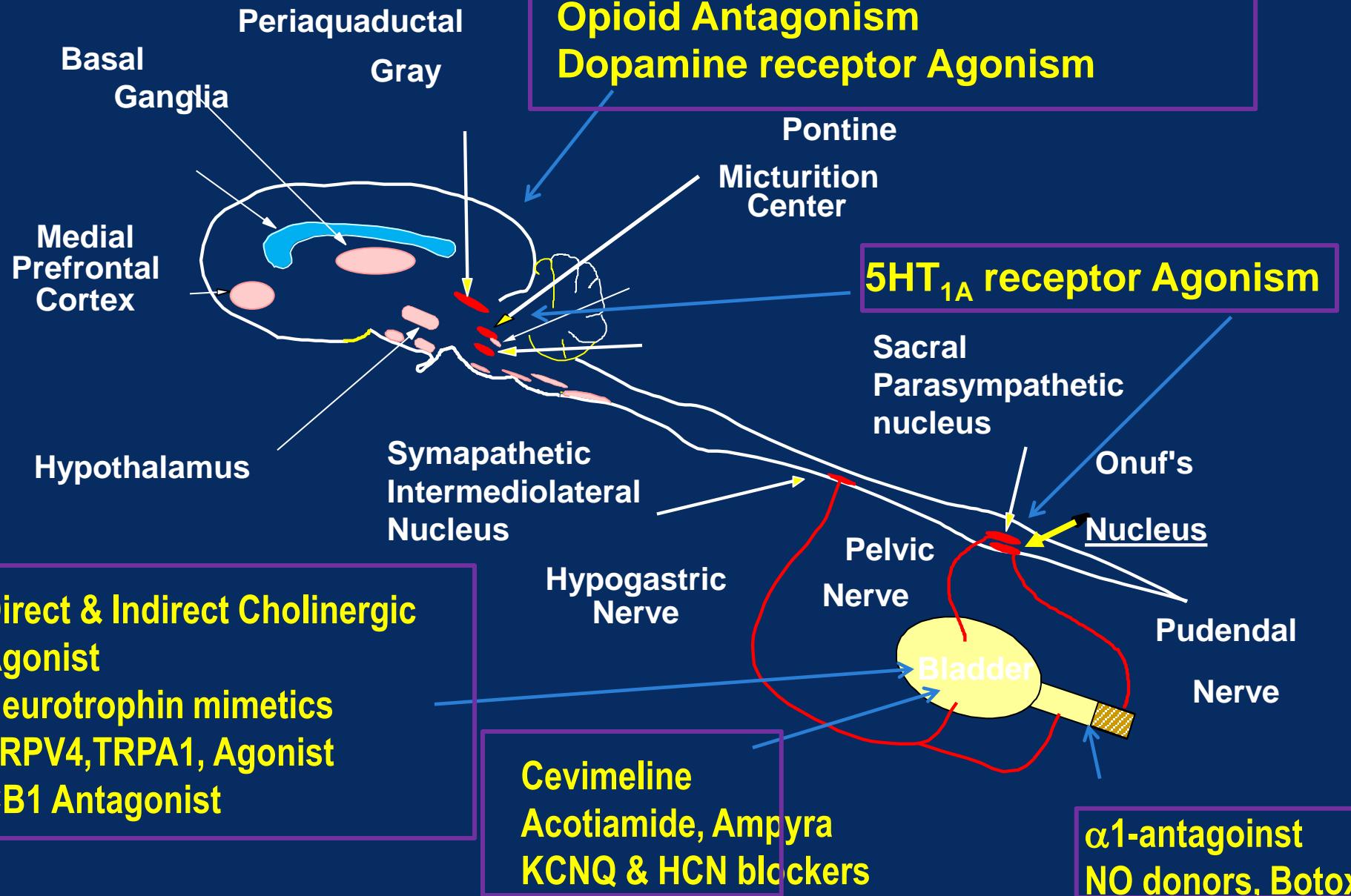
## ¶ Peripheral Acting Mu Opioid Receptor Antagonists (Pegylated Naloxone)

- ¶ Naloxone blocks the inhibitory action of the enkephalins on voiding
- ¶ Naloxone raised detrusor pressure of acute spinal shock patients during CMG
- ¶ Naloxone diminished pelvic floor EMG activity in 10 detrusor areflexic patients from 4 month old lower level SCI

J Urol. 1987 ; 137(6):1202-5

Ann Clin Res. 1982 Apr;14(2):98-102

# Summary





University of Pittsburgh

# THANK YOU!

